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Energy Landscape and Dynamics of Biomolecules
Extended Abstract

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Abstract. Proteins are not isolated homogeneous systems. Each protein can exist in a very large number of conformations (conformational substates) that are characterized by an energy landscape. The main conformational motions, similar to the α and β fluctuations in glasses, are linked to fluctuations in the bulk solvent and the hydration shell.

Key words: protein energy landscape, protein dynamics, protein fluctuations, alpha and beta relaxations, slaving

Goals of Biological Physics

The number and diversity of biological systems is so large that description and classification alone cannot lead to a fundamental understanding. Biological physics can help by establishing concepts and laws that are valid for a wide range of biological systems. Atomic, nuclear, and condensed matter studies have taught physicists that many concepts emerge from looking at the structure, the energy levels, and the dynamics of systems. As an example, consider atoms. The Balmer series, the Bohr atom, and the Schrödinger equation were crucial steps in arriving at a quantitative and fundamental understanding of atoms. Can we find similar phenomena in the physics of biomolecules? We believe that it is possible. The following notes sketch some of the progress that has already been made by connecting structure, energy levels, and dynamics.

The Structure of Proteins

Proteins are the building blocks of biology. They work as structural elements, as storage and transport systems, and as catalysts. In effect, they perform most of the tasks in living systems [1]. While the first structure determinations, using X-ray diffraction, by Max Perutz and John Kendrew, took many years, protein structures are now routinely produced at a frightening rate. The determination of the structure of any protein that can be crystallized is no longer a problem. The structure of

proteins that cannot be crystallized can be determined using NMR [2]. The position of hydrogen atoms, which cannot easily be seen with X-rays, can be found by using neutron diffraction [3]. The average structure of a large number of proteins is now known and can be looked up in the protein data bank.

The Energy Landscape

The beautiful pictures of proteins in books and journals give the impression that proteins exist in unique structures. Nothing could be further from the truth. Experiments and computations show unambiguously that a given protein can assume a large number of somewhat different conformations (conformational substates) [4–6]. The substates can be described by the energy landscape, possibly the most important concept for bringing order into the vast amount of information available on the structure, dynamics, and function of biomolecules. The energy landscape is a construct in $\approx 3\ N$ dimensions, where N is the number of atoms forming a biomolecule and its immediate surrounding. A particular conformation is represented by a point in this hyperspace. Studies using a broad array of techniques, from flash photolysis to X-ray diffraction, the Mössbauer effect, neutron scattering and spectral hole burning, have shown that the conformational substates indeed exist and are organized in a hierarchy of a number of tiers [7].

Protein Dynamics

To carry out their functions, most proteins must perform motions. These motions can either be thermal equilibrium fluctuations or non-equilibrium relaxations, caused for instance by reactions. In terms of the energy landscape, motions can be described as jumps of the system from substates to substates. A task of biological physics is the experimental study of these motions, their connections to structure, and to the energy landscape. Since the rate coefficients of fluctuations range from fs^{-1} to s^{-1} or possibly even less, it is clear that many different tools are needed. Moreover, to understand the motions, experiments over broad ranges of times, temperatures, pressure, and solvent conditions will are required. The small temperature range often used is not sufficient to distinguish for instance between Arrhenius and non-Arrhenius type motions.

Before describing surprising features of fluctuations in proteins, a few remarks concerning dynamic processes in glasses are appropriate [8]. Glasses are inhomogeneous like proteins and can be described by an energy landscape [9, 10]. Two processes in glasses are relevant for the discussion of protein dynamics: glasses show two major relaxation processes, called α and β. The α relaxations describe large-scale fluctuations; they often are not exponential in time. Instead their time dependence can be approximated by a stretched exponential,

$$\Phi_\alpha(t, T) = \exp\{-[k(T)t]^\beta\}.$$

They usually do not follow an Arrhenius relation in temperature, but the rate coefficient $k(T)$ can be approximated by the Vogel-Tammann-Fulcher relation,

$$k_\alpha(T) = A \exp\{-H/k_B(T - T_0)\}.$$

The β relaxation is also often nonexponential in time, but can be approximated by an Arrhenius relation. The preexponential factor is, however, usually larger than 10^{13} s^{-1}, indicating that the β relaxation is not a simple over-the-barrier process. While the α relaxations become immeasurably slow below the glass transition temperature T_g, the β relaxation can be followed far below T_g. (T_g is usually defined as the temperature where $k_\alpha(T_g) = 10^{-2}$ s^{-1}).

It has been known for some time that proteins share properties with glasses [11]. Recent studies show that the similarity has unexpected aspects, related to the interaction of the protein proper with the bulk solvent and with its hydration shell. Consider first the α relaxation. A comparison of the rate coefficients, $k_p(T)$, for large-scale motions in proteins, for instance entry and exit of ligands [4, 12], with the rate coefficient $k_\alpha(T)$ of the bulk solvent shows that they have the same temperature dependence over many orders of magnitude. In other words, large-scale fluctuations of the protein are **slaved** to the fluctuations in the bulk solvent. These protein processes are controlled by enthalpy barriers in the solvent, not by protein-internal enthalpy barriers [13, 14]. But a puzzle appears: while $k_p(T)$ and $k_\alpha(T)$ have the same temperature dependence, for some processes $k_p(T)$ is 10^5 times slower than $k_\alpha(T)$! What causes this slowing? It obviously must be entropy or, in other words, the large number of states in the protein. Here is where the energy landscape comes in. A process like the exit of a ligand is not like opening a rigid door. Many sidechains must be in the right position, helices may have to move. Opening thus corresponds to a random walk in conformation space. Indeed, theory supports such a picture [15]. Significant properties of proteins follow from these experimental results: proteins work in close interaction with their environment, the environment controls the enthalpy barriers for large-scale motions; the protein proper contributes the entropy as characterized through the energy landscape.

Protein dynamics is controlled not only by α fluctuations but also by β fluctuations [16, 17]. Moreover, the hydration shell is crucial for the dynamics; dehydrated proteins do not function. It has been known for a long time that carbon monoxide can move through hydrated myoglobin even if the protein is embedded in a rigid environment such a PVA or ice [4]. The fluctuations that permit these motions thus cannot be slaved. Reanalyzing mean-square displacement data from neutron scattering and Mössbauer experiments implies that these fluctuations have properties characteristic of β fluctuations. The data also suggest that the "dynamic transition" claimed to occur in proteins near $T_d \approx 200$ K is an artifice; β fluctuations continue smoothly below T_d.

A complete understanding of the energy landscape and of the related fluctuation and relaxation processes is still a dream, but it is a grand challenge for biological physics.

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